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Accelerated thermal reaction kinetics by indirect microwave heating of a microwave-transparent substrate†

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Macroscopically homogeneous mixtures of *p*-nitroanisole (*p*NA) and mesitylene (MES) can be selectively heated using microwave (MW) energy. The *p*NA solutes agglomerate into distinct phase domains on the attoliter-scale (1 aL = 10^{-18} L), and these agglomerates can be MW-heated selectively to temperatures that far exceed the boiling point of the surrounding MES solvent. Here, a 1 : 20 mixture of *p*NA : MES is used as a mixed solvent for aryl Claisen rearrangement of allyl naphthyl ether (ANE). ANE itself does not heat effectively in the MW, but selective MW heating of *p*NA allows for transfer of thermal energy to ANE to accelerate rearrangement kinetics above what would be expected based on Arrhenius kinetics and the measured bulk solution temperature. This focused study builds on prior work and highlights 1 : 20 *p*NA : MES as a mixed solvent system to consider for strategically exploiting MW-specific thermal effects.

Introduction

Microwave (MW) heating is an enabling technology for organic synthesis,[1] providing many practical advantages associated with rapid and efficient heating of reaction mixtures. Beyond the well-established tactical benefits, there is interest in strategic application of MW heating to alter reaction outcomes compared to conventional heating.[2] The nature of MW-specific thermal effects remains a topic of debate,[3] but a growing body of evidence[4] makes clear that MW heating can produce outcomes that deviate from predictions based on classic Arrhenius kinetics and the measured temperature of the bulk solution (Fig. 1).

Our labs have identified several examples of organic reactions for which MW heating outperforms conventional heating in terms of reaction rate[5] and/or yield,[6] and one system (Fig. 1d) in which the coordinated application of MW and conventional heating was better than either heating method individually.[7] These observations are consistent with selective MW heating of polar components within systems that are otherwise MW-transparent. Our central design hypothesis is that polar solutes agglomerated in nonpolar solvent can be selectively heated with MW energy, creating dynamic temperature profiles that cannot be replicated with conventional heating; selective heating can result in thermal reaction kinetics and dynamics for the polar solute that deviate from what would be expected based on the measured solution temperature. The generalization of this phenomenon to reaction systems potentially represents a paradigm shift in how synthesis is accomplished.

Selective MW heating can be observed spectroscopically.[8] When selective MW heating differentially impacts molecular components of a solution, temperature differences (ΔT) can be quantified by measuring the temperature-dependent Stokes and anti-Stokes bands in the Raman spectra.[9,10] We looked at mixtures of *p*-nitroanisole (*p*NA, polar) and mesitylene (MES, nonpolar) by *in situ* Raman spectroscopy during and after MW heating.[11] Under dynamic microwave heating, the measured temperature of *p*NA exceeded that of MES by as much as 114 °C. Notably, the temperature difference persisted for many seconds (>2 min) after the MW source was turned off. These observations can be explained by considering agglomerates of polar solutes within the bulk solvent. These agglomerates must be large enough that heat transfer from *p*NA to MES occurs predominantly by (slow) convective heat-transfer as opposed to (much faster) thermal conductance. The persistence of a large ΔT was modeled computationally by adding a thermal conductance insulation layer between the solute agglomerate and bulk solvent, which suggests that super-heated agglomerates vaporize the surrounding solvent to create a solvent vapor barrier around the agglomerate (Fig. 2).[12] Finally, we were able to detect these agglomerates by small-angle neutron scattering and estimate their size as spheres to be on the order of 60 nm in

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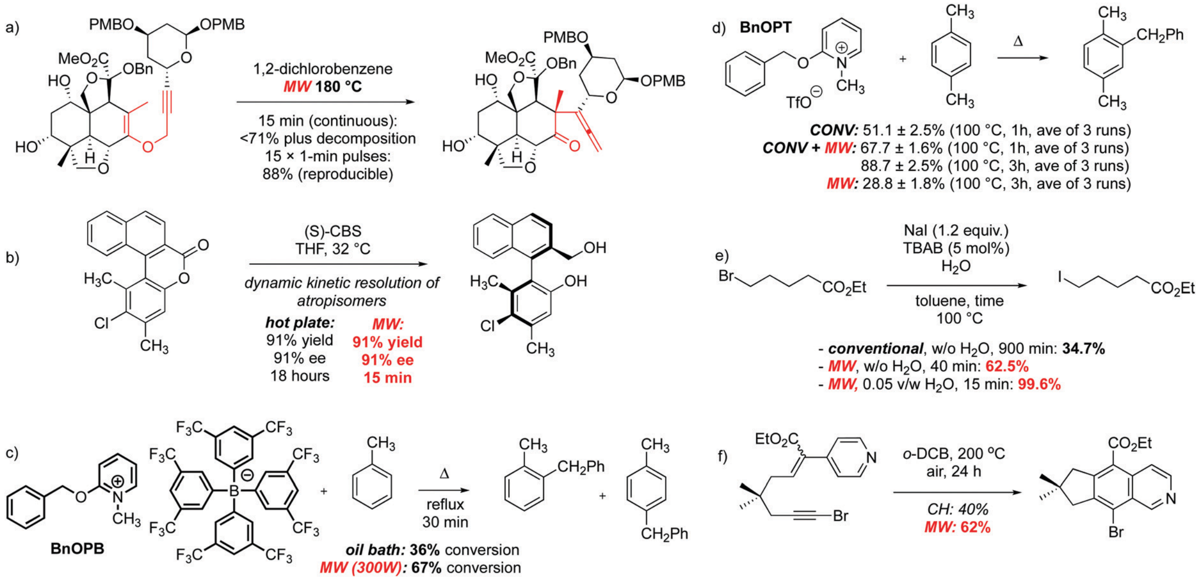

Fig. 1 Examples of altered reaction outcomes under MW heating compared to conventional heating.

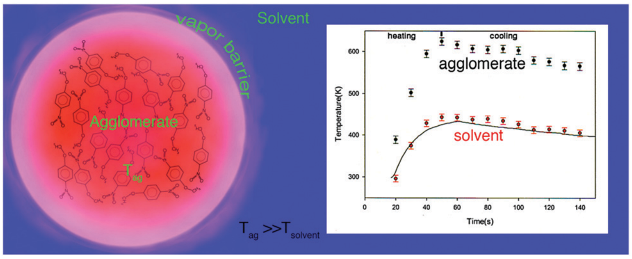

Fig. 2 Right: Schematic illustration of polar *p*NA agglomerate and insulating vapor barrier under MW irradiation. Left: Selective MW heating of *p*-nitroanisole (*p*NA, polar) and mesitylene (MES, nonpolar) as measured by *in situ* Raman spectroscopy. See ref. 8.

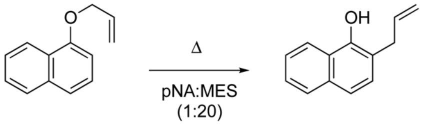

Fig. 3 Claisen rearrangement of allyl naphthyl ether (ANE) in 1 : 20 *p*-nitroanisole : mesitylene (*p*NA : MES); See ESI† for additional details.

radius, which corresponds to a spherical volume of about 1 attoliter (10^{-18} L).

We reasoned that any thermally reactive solute that coalesces with polar solutes into one of these attoliter-sized agglomerates would react according to the temperature of the agglomerate, as opposed to the temperature of the bulk solution. If local heat generated within the agglomerates were transferred to reactive solute molecules more efficiently than to the bulk solution, then selective MW heating of that reactive solute would be achieved independent of direct interactions of the reactive solute with MW energy. In other words, a reaction can be MW-accelerated even if the substrate itself does not absorb MW energy.[13]

Testing this hypothesis, we examined aryl Claisen rearrangements of allyl naphthyl ether (ANE)[14] in a mixture of *p*NA and MES (1 : 20 mole ratio) (Fig. 3). We observed that MW heating accelerated the Claisen rearrangement of ANE in 1 : 20 *p*NA : MES over what would be predicted based on measuring the bulk solution temperature. ANE itself is poorly MW-absorbing; MW heating of *p*NA is the primary source of thermal energy in solution (Fig. 4). We also found that *p*NA accelerates the Claisen rearrangement of ANE in MES under conventional heating, consistent with known solvent effects in the aryl Claisen rearrangement[15] and the hypothesis that the reaction can occur within the polar *p*NA agglomerate. We conclude that ANE can partition between the agglomerates and the bulk solution; Claisen rearrangement is faster in the agglomerates than in the bulk; and selective MW heating of the agglomerates further

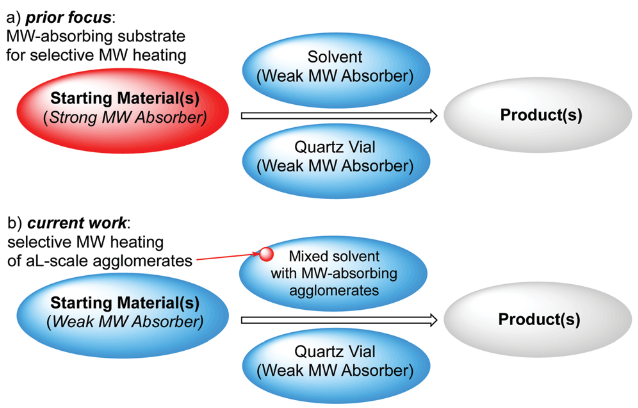

Fig. 4 Conceptualized depictions of selective MW heating as applied in (a) prior work and (b) the current study.

accelerates thermal reaction kinetics beyond what is observed under conventional heating.

Conventional heating experiments

We prepared a stock solution—solution **A**—comprising a mixture of 1 : 20 *p*NA : MES (mole ratio), to which was added 0.1 mmol each of ANE and diphenylmethane (DPM, internal standard) per milliliter of *p*NA:MES. This homogeneous stock solution (**A**) facilitated sample preparation and ensured that identical samples were used for each experiment. Samples of solution **A** were heated conventionally (oil bath) or in a MW reactor; solution temperatures were measured using internal probes.

Identical 3.0 mL samples from solution A were heated in a silicone oil bath at seven different temperatures between 130 °C and 160 °C in 5 °C increments using 10 mL MW-compatible tubes. The oil bath temperature was controlled using the built-in thermocouple of the heater, which was calibrated to within ±1 °C. Actual solution temperatures were recorded more precisely using an internal fiber optic probe that was calibrated to within ±0.1 °C and was consistent with the fiber optic probe available in the microwave instrument (see ESI,† Section S2). Samples were heated over 1, 2, and 3 h for reactions at 145–160 °C, and samples were heated over 3, 5, and 6 h for reactions at 130–140 °C to realize higher conversion at the lower reaction temperatures. Three identical samples were heated for each temperature and reaction time. For example, nine separate reactions were conducted at 150 °C to collect data after 1, 2, and 3 h for kinetic analysis: three independent samples of ANE (3.0 mL solution A) were reacted for 1 h, and the concentration of each determined by quantitative NMR[16] (qNMR, see ESI,† Section S5), then three fresh samples taken from the same stock solution were reacted for 2 h and the concentrations determined, and this procedure was repeated for 3 h. The natural log of the average concentrations of ANE from each set of three experiments was plotted against time at each temperature to give the corresponding rate constants (Fig. 5a, also see ESI† Section S4 for more details). To determine the parameters of the Arrhenius equation, the rate constants were fit to the logarithmic form (Fig. 5b), yielding an activation energy for this Claisen rearrangement of E_a = 127.46 ± 2.39 kJ mol^{-1} with a pre-exponential term of A = (4.05 ± 3.01) × 10^{13} min^{-1}.

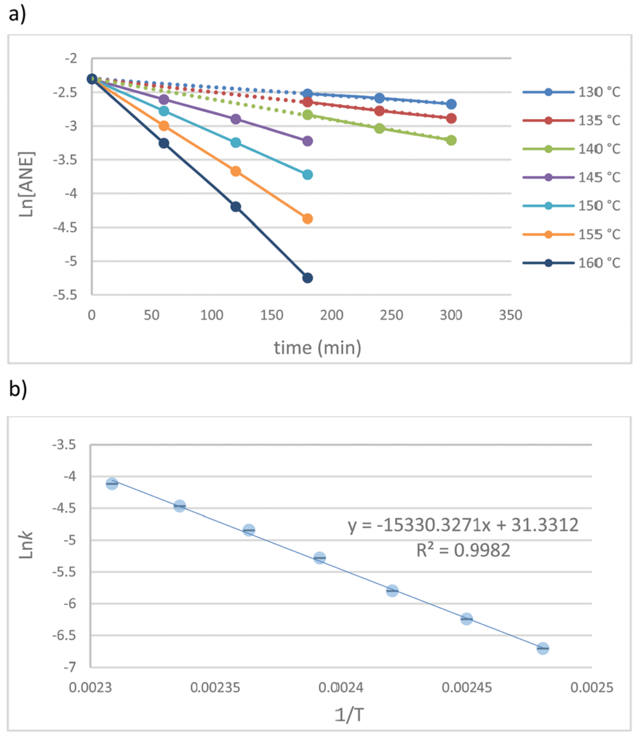

Fig. 5 (a) First order kinetic plots of ANE concentrations *vs.* time at various temps from 130–160 °C. (b) Arrhenius rate constant data.

Microwave heating experiments

The choice of heating mode in microwave experiments can have a significant impact on selective microwave heating.[5c] We focused here on pulsed heating—cycles of periodic heating at constant MW power (typically 300 W) with intermittent cooling—to maximize the temperature differential between the agglomerate domains and bulk solvent over extended reaction times. We envision that selective MW heating occurs during the heating phase of the cycle, creating a temperature differential (ΔT) between the agglomerates and the bulk that persists into the cooling phase. The rearrangement reaction proceeds throughout the process at rates that vary as a function of local temperature. Enhanced conversion over time under MW heating supports the hypothesis of selective MW heating and the postulate of a persistent ΔT for discrete solution components. For academic reasons, we consider data from the heating and cooling phases both together and separately (*vide infra*). Three temperature ranges were considered and run in triplicate for 300 cycles: 50–130 °C, 50–140 °C, and 50–150 °C. As the higher setpoint temperature increased (*i.e.*, from 130 °C–140–150 °C), it took longer for each cycle to be completed, thus requiring more time for the entire set of cycle. Reactions having higher maximum set temperatures also spent more time in the cooling phase (for complete details see ESI,† Table S6). Expected yields for each reaction based on Arrhenius kinetics were predicted (x_{pre}) using the measured temperature and its associated rate constant and the integrated first-order rate law to calculate the reaction conversion over each second, then summing these predicted conversions over all seconds (see ESI,† Section S7). The yields predicted based on the measured bulk solution temperature deviated significantly and consistently from the actual yields (x_{act}) as determined by qNMR. Whereas these experiments were conducted under variable temperature conditions, we determined what hypothetical fixed temperatures would be required to achieve the same actual and predicted yields in constant temperature experiments. The constant temperature required to achieve the same actual yield under conventional heating as was observed under pulsed MW

Table 1 The average ratios of k_{eff}/k_{CH} and k_{MW}/k_{CH} at three temperature ranges for 300-cycle pulsed heating experiments

Temp. range (°C)	Ave. k_{eff}/k_{CH}	Ave. k_{MW}/k_{CH}
50–130	1.419 (± 0.037)	3.278 (± 0.188)
50–140	1.392 (± 0.058)	2.455 (± 0.211)
50–150	1.294 (± 0.022)	1.657 (± 0.042)
50–130[a]	1.567 (± 0.065)	3.524 (± 0.277)

[a] 900 cycles of pulsed heating.

heating is the "effective temperature" of the pulsed heating experiments, and it corresponds to an effective rate constant of k_{eff}. Likewise, we calculated the constant temperature and corresponding rate constant (k_{CH}) required to achieve the predicted yield based on the measured temperature in the absence of selective MW heating. The ratio of k_{eff}/k_{CH} was then determined by eqn (1) (see ESI,† Section S10 for full details).

$$k_{eff}/k_{CH} = \ln(1 - 0.01x_{act})/\ln(1 - 0.01x_{pre}) \qquad (1)$$

In other words, the ratio k_{eff}/k_{CH} provides a direct measure of the impact of selective MW heating on these pulsed heating experiments. The average ratios for these pulsed heating experiments are summarized in Table 1. In this case, we observed a *ca.* 40% rate increase for the 50–130 °C range compared to what would be expected based on Arrhenius kinetics.

Another approach to analyzing these data is to consider separately the effective rate constant during those periods of time that the MW reactor is on: k_{MW}. In the absence of persistent ΔT associated with insulated, superheated agglomerates, one would expect reaction kinetics in solution to conform with Arrhenius predictions based on bulk solution temperature when the MW reactor is off. If we assume, for purposes of academic discussion, that the reaction behaves conventionally with respect to bulk solution temperature when the MW reactor is off, then we can subtract the reaction conversion calculated to occur during these times and focus on the conversion that occurs during periods of MW heating. By this alternative analysis, we calculate a >3-fold rate increase (k_{MW}/k_{CH}) for the 50–130 °C range during the MW heating phase. This alternative analysis suggests that reducing the time needed for the cooling phase would enhance the impact of selective MW heating on reaction rate.

The yield of product as estimated by qNMR was 22% after 300 cycles in the 50–130 °C temperature range. We repeated these experiments over 900 cycles to target higher conversion ($\geq 50\%$). After 900 cycles, we observed a similar, if not slightly higher,[17] rate increase: $k_{eff}/k_{CH} = 1.567 \pm 0.065$ ($k_{MW}/k_{CH} = 3.524 \pm 0.277$). As before, these experiments were run in triplicate using pre-made solution **A**. One of the 900-cycle experiments in the 50–130 °C temperature range took 1957.3 min (*ca.* 32.6 h) and produced 57.3% conversion of ANE as estimated by qNMR. By comparison, the expected conversion as predicted using Arrhenius parameters and the bulk measured temperature was 41.76%. The hypothetical fixed temperatures required to replicate these conversions at the same time point are 118.8 °C and 114.2 °C, respectively. Thus, the effective temperature of the ANE solute, despite being largely nonpolar and MW-transparent, was approximately 4.6 °C above the bulk temperature.

Table 2 Summary of data for fixed power experiments

Entry	Power (W)	Duration (min)	Ave./final T (°C)	k_{eff}/k_{CH}
1	145	300	125.10/126	1.318
2	170	300	132.88/133	1.211
3	200	300	143.52/145	1.145
4	250	120	154.49/160	1.160

We cross-checked our observations using alternative experimental designs and controls. We heated a sample of solution **A** conventionally at 119 °C for 1913.6 min (*ca.* 31.9 h) and observed 57.7% conversion by qNMR, which aligns well with the 57.3% conversion observed for the aforementioned 900-cycle MW heating experiment. Likewise, heating at 114 °C for 1978.4 min (*ca.* 33.0 h) produced 42.5% conversion by qNMR. These observations from conventional experiments support the validity of the hypothetical fixed temperatures discussed in the previous paragraph and the conclusion that ANE reacted in accord with an effective temperature higher than the bulk solution temperature by virtue of selective MW heating.

We reported previously that pulsed MW heating can be more effective than constant MW power or constant temperature at selective MW heating.[5c] A small set of experiments here (Table 2) using constant MW power align with these prior conclusions.

We heated 3.0 mL volumes of solution **A** for 300 min (5 h) at MW powers from 145 W to 200 W, and at 250 W for 120 min (2 h). We observed rate increases of *ca.* 15–30% based on the k_{eff}/k_{CH} ratio using constant power MW heating, compared with rate increases up to *ca.* 40% observed with pulsed heating (*cf.* Table 1). The kinetic advantage of pulsed MW heating is observed despite the MW reactor being off most of the time during the pulsed heating experiments (see also the estimated >3-fold rate increase for times when the MW reactor was on, *vide supra*). Perhaps most remarkable about all of these MW-specific rate enhancements is that the ANE substrate itself is largely MW-transparent—control experiments using ANE in pure MES (without *p*NA) under MW heating fail to produce sufficient heat for observable conversion of ANE to take place.

Conclusions

In summary, a solution of 1 : 20 *p*NA : MES (mole ratio) is subject to selective MW heating and can transfer heat differentially to solutes that themselves do not effectively absorb MW energy. Our interpretation of the observations reported herein is that ANE can partition into the agglomerated *p*NA, where the local temperature is higher than the bulk solution and the aryl Claisen rearrangement is accelerated. The ability to create dynamic and locally differentiated temperature profiles in solution-phase reaction systems has implications for Green

Chemistry and for strategic applications of MW heating in chemical synthesis.

Experimental section

All commercial reagents and solvents were used directly without additional purification. Syringes were used in all protocols requiring the transfer of a liquid reagent. Column chromatography was performed on 60 μm Sfär silica gel columns using Biotage Isorela flash chromatography system. ^{1}H NMR and ^{13}C NMR spectra were registered on a 400 MHz JEOL spectrometer to conduct ^{1}H and ^{13}C NMR spectroscopy in $CDCl_3$ ($\geq$99.8 atom% D, contains 0.03% (v/v) TMS) purchased from Cambridge Isotope Laboratories. Chemical shifts were reported in units (ppm) referenced to 0.0 ppm of TMS in the ^{1}H spectrum and 77.0 ppm of $CDCl_3$ in the ^{13}C spectrum. All coupling constants were reported in Hertz (Hz).

Preparation of allyl 2-naphthyl ether (ANE)

To a stirred solution of 1-naphthol (7.28 g, 50.0 mmol) in acetone (250 mL, 0.2 M) were added K_2CO_3 (14.0 g, 16.1 mmol, 2.0 equiv.) and allyl bromide (5.2 mL, 60.0 mmol, 1.2 equiv) at room temperature under air. The mixture was then heated at reflux for 2 hours, cooled down to room temperature, filtered using Celite through a pad of $MgSO_4$, and concentrated by rotary evaporation. The resulting residue was purified by silica gel flash chromatography (5–20% EtOAc/Hexanes) to afford 9.03 g of ally 2-naphthyl ether as a light yellow oil (98% yield). The characterization data matched the previous reports in the literature.[18]

Preparation of stock solution A

Ally 2-naphthyl ether (ANE, 7.37 g, 40.0 mmol), 4-nitroanisole (*p*NA, 22.0 g, 144 mmol), diphenylmethane (DPM, 6.73 g, 40.0 mmol; internal standard), mesitylene (MES, 400 mL) were mixed together and stirred for 1 hour.

Author contributions

AT: investigation, methodology, formal analysis, data curation, and writing original draft; AES: conceptualization, funding acquisition, and project administration; GBD: conceptualization, funding acquisition, project administration, methodology, supervision, resources, and writing review and editing. All authors have agreed to the publication of this manuscript.

Conflicts of interest

The authors declare no competing financial interest.

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12 The *p*NA temperature as measured by Raman spectroscopy could exceed the boiling point of MES (165 °C) by more than 100 °C, so vaporizing the neighboring solvent was perhaps to be expected.

13 We tested an earlier version of this hypothesis in aryl Claisen rearrangements of allyl phenyl ether, refined here to incorporate new information about the agglomeration phenomena, and dubbed it ''the chaperone effect''; see ref. 5*d*.

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